

Anaemias: classification and conservative treatment

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Avoiding transfusion...

Anaemia is a symptom and
not a diagnosis!

i.e.: consequence of something and not a disease per se

Erythropoiesis – physiology

ερυθροζ (gr.): red; *ποιησιζ* (gr.): production, generation

BFU_E



CFU_E



Proerythroblast (E1)



Basophil macroblast (E2)



Polychromatic macroblast (E3)



Polychromatic normoblast (E4)



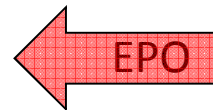
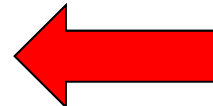
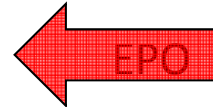
Orthochromatic normoblast (E5)



Reticulocyte



Red blood cell



- E1↑↑
- E1 → reticulocyte: 5 days,
EPO effect: 2 days.

1 E1 → 16 RBC

Erythropoetin (EPO) I.

- Classic hormon: acts far from the site of its production, negative feed-back
- Produced by renal peritubular fibroblasts (90%) (in 10% it's produced by the liver)
- 30.4 kD, 165 aminoacids and 4 CH chains, 60% of its is peptid, the rest is CH

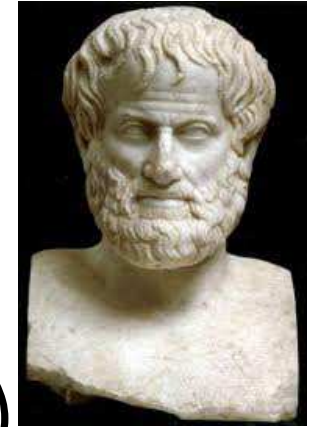
Erythropoetin (EPO) II.

- Production is increased by tissue hypoxia, this depends on:
 - O_2 tension of the surrounding air (high altitude)
 - O_2 tension of the arterial blood (cardiorespiratory functions)
 - Haemoglobin concentration
 - Haemoglobin O_2 affinity
 - Renal arterial blood flow (polycystic kidney, hydronephrosis)
 - Renal O_2 consumption
- EPO level can increase by 2-3 logs!
- Effector cells: BFU_E , $CFU_E \rightarrow RBC \uparrow, Hb \uparrow$

Erythropoetin (EPO) III.

- Factors suppressing endogenous EPO production:
 - decrease of renal parenchyma:
 - renal failure
 - cytokin effect (TNF, IL-2, IFN):
 - inflammation
 - infection
 - tumor burden
 - direct deterioration of peritubular cells:
 - chemotherapy (platina-derivates)

Definition of anaemia



- $\alpha\nu$ | $\alpha\iota\mu\alpha$ (*Aristotle, Historia Animalium*)
- Decrease of haemoglobin concentration, haematocrit or red blood cell count below the normal level
- Hgb: < 135 g/l (male); < 120 g/l (female)
Htc: < 0.40 (male); < 0.37 (female)

WHO classification of anaemia based on haemoglobin level (g/l)

- Grade 0: ≥ 110 normal
- Grade 1: 95-109 mild
- Grade 2: 80-94 moderate
- Grade 3: 65-79 severe
- Grade 4: < 65 life-threatening

Anaemia – complaints and symptoms

- Complaints
 - weakness, intolerance for physical exercise
 - somnolence
 - effort dyspnoea, tachycardia, angina
 - dizziness, tinnitus
 - loss of appetite
- Symptoms
 - paleness (skin, mucous membranes)
 - tachycardia, hypotonia
 - heart failure
 - visual disturbances, psychiatric symptoms

Tolerance for anaemia

- Level of anaemia
- Age
- Concomittant diseases (eg. cardiovascular, pulmonary)
- Speed of the development of anaemia
(compensation: 2,3 DPG \uparrow \rightarrow maintaining tissue oxigenisation)

Useful laboratory tests

- CBC (RBC, Hgb, Htc, WBC, PLT)
 - Reticulocyte (ratio and absolute count)
 - MCV, MCH
 - Peripheral blood smear – cytomorphology
 - SeBi, LDH
 - ESR, CRP
 - SeFe, Tf, Sat, SolTfR, Ferritin
 - FOBT, urine sediment
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- B₁₂, folic acid
 - Direct Coombs test, irregular antibodies
 - Haptoglobin, plasma free haemoglobin
 - Erythropoetin
 - Serum total protein, ELFO
 - Bone marrow (cytology, Prussian-blue, FACS, cytogenetics)
 - Hgb ELFO

Classification of anaemias based on etiology

- Aregenerative – decreased production
- Regenerative – increased destruction
- Bleeding
- Problems of distribution

Aregenerative – decreased production

- Erythropetic stem cell defect (aplastic anaemia, BM infiltration (precursor↓), myelodysplasia)
- Disorders of DNA synthesis (megaloblastic anaemia: deficiency of B₁₂, folic acid)
- Disorders of Hgb synthesis (iron deficient anaemia)
- Deficiency of erythropoetin (renal anaemia)

Regenerative – increased destruction

- Intrinsic RBC defects (corpuscular haemolytic anaemias)
 - Membrane defects
 - Enzyme defects
 - Haemoglobinopathies
- Extrinsic causes (extracorporeal haemolytic anaemias)
 - Allo-/autoantibodies
 - Drugs
 - Infections
 - Thrombotic microangiopathies (TTP/HUS, HELLP)
 - Physical-chemical harms
 - Metabolic disorders
 - Rare causes

Bleeding and distributional problems

- Acute blood loss
 - Anaemia due to bleeding
- Problems of distribution
 - Sequestration in enlarged spleen: hypersplenism
 - Pregnancy

Classification of anemias based on RBC size (MCV) and MCH

- Hypochrom microcytic (MCH↓, MCV↓)
- Normochrom normocytic (MCH→, MCV→)
- Hyperchrom macrocytic (MCH↑, MCV↑)

Hypochrom microcytic anaemias

- Iron (Fe) \uparrow / \rightarrow
 - Thalassaemia
 - Myelodysplastic syndrome
- Iron (Fe) \downarrow , ferritin \downarrow
 - ***Iron deficient anaemia***

***Mentzer-index: MCV/RBC;
<12: Thalassaemia***

Normochrom normocytic anaemia

- Reticulocyte ↑

- Haemolytic anaemia
- Bleeding anaemia

NB!: in case of high reticulocyte MCV ↑

- Reticulocyte ↓

- Aplastic anaemia
- BM infiltration (lymphoma, leukaemia, tumor)
- ***Renal anaemia***
- ***ACD, anaemia of chronic disease***

Hyperchrom macrocytic anaemia

- Reticulocyte →/↓
 - ***Megaloblastic anaemias (deficiency of B₁₂, folic acid)***
 - Myelodysplastic syndrome

Iron metabolism I.

- Daily iron loss: male 1 mg, young female 2 mg, pregnant/breast feeding female 3 mg
- Iron stores: **male 50 mg/bwkg, female: 35 mg/bwkg**
- Iron stores
 - Haem-iron – 70%
 - Storage iron (ferritin and haemosiderin) – 18%
 - Functional iron (myoglobin and enzymes) – 12%
 - Transport iron (binded to transferrin) – 0.1%
- 1 g hgb: 3,4 mg Fe; **1 ml blood: 0.5 mg Fe**

Iron metabolism II.

- Absorption
 - Proximal small intestine (<10% → 25%)
 - Fe²⁺
 - Transport of iron: transferrin (approx. iron content 3 mg)
 - Hepcidin, ferroportin
- Reutilisation [RES; *reuse*: haem/myoglobin/enzymes]
 - Daily iron need of erythropoiesis: 20-25 mg → volume of reutilisation is 80-85%!
- Storage
 - Intracellular *ferritin* (water soluble: apoferritin + ferro-hydroxy-phosphate micells) and *haemosiderin* (non-water soluble, lysosomes developing due to autophagocytosis)
 - Liver, BM, other tissues

Iron deficient anaemia (IDA) I.

- Europe: 10% of reproductive females; developing countries: 50% of population; worldwide 25%
- 80% of all anaemias, 80% of IDA cases are females!
- Etiology:
 - *Primary:* long lasting disbalance between necessity and intake without underlying disease (infants, children, adolescents, pregnant, breast-feeders, elderly, vegans)
 - *Secondary:*
 - **Chronic bleeding (80%!)**
 - Decreased absorption (resection of stomach, malabsorption (coeliac disease))
 - Problems of iron mobilisation and transport (ACD)

Iron deficient anaemia (IDA) II.

- Blood (haemoglobin) loss
 - Genital bleeding of females
 - GI tract
 - Other sources (urogenital, oropharynx, gums, nose, lung)
 - Bleeding due to surgery and trauma
 - Haemodialysis, frequent blood sampling, blood donation
 - Intravasal haemolysis → haemoglobinuria
 - Artefacts (Münchhausen sy.)

Iron deficient anaemia (IDA) III.

- Skin and mucous membrane symptoms: striated nails, koilonychia, fragile nails and hair, hair loss, dry skin, itching
- Plummer-Vinson sy.: iron deficient mucous membrane atrophy
- Aspecific neuro-psychiatric symptoms: headache, decreased ability to concentrate, irritability, „restless leg”, pica
- General anaemic symptoms

Iron deficient anaemia (IDA) IV.

- Prelatent iron deficiency
 - Ferritin↓ and BM iron storage ↓
- Latent iron deficiency (iron deficient erythropoiesis)
 - + SeFe↓, TF↑, sTfR↑, Sat↓, >10% microcytes
- Overt iron deficiency = iron deficient anaemia (IDA)
 - + Hgb↓, Vvs↓, Htk↓, RBC morphology (aniso-poikilocytosis, microcytes), thrombocytosis!

Iron deficient anaemia (IDA) V.

- ***Not a disease per se, but a consequence → Search for the cause!***
- Therapy
 - Oral: 100-200 mg Fe²⁺/die, fasting, 2× daily; overdose impossible (haemochromatosis) – during 3-6 months; improvement of CBC after one week
 - Parenteral (IBD, malabsorption – test of iron absorption!, intolerance): iron gluconate (Fe³⁺) ; allergy, overdose; ***does not act faster!***

Iron need (mg) = lack of Hgb (g/dl) × body weight (kg) × 3

Prophylactic iron supplementation during pregnancy, breastfeeding and for prematures

Anaemia of chronic disease (ACD) I.

- Normochrom (75%) or hypochrom (25%), RDW
- Underlying: inflammation, infection, tumor
- Macrophage activation
 - RBC lifetime decreases
 - Iron stored in macrophages
(SeFe↓, TF↓, Ferritin↑)
- EPO↓ (absolute/relative) – cytokin effect
- BFU_E and CFU_E blockade – cytokin effect
- Blood loss

Anaemia of chronic disease (ACD) II.

- In case of malignant diseases:
 - BM infiltration
 - Chemotherapy
 - Suppression of EPO production
 - Direct myelotoxicity
 - Radiation therapy
 - Direct myelotoxicity

Renal anaemia

- Decreasing EPO production paralelly with the decreasing renal parenchyma
- Decrease of GFR resulting azotaemia (~BUN 20 mmol/l, ~creatinin 300 μ mol/l, GFR 30 ml/min/m²)
- Normocytic, normochrom anaemia, generally moderate
- Additive effects of other factors:
 - Iron deficiency (haemodialysis)
 - ACD (uraemia is a chronic toxic condition!)
 - Infection (Cimino-fistule, CAPD)
 - Aluminium intoxication

Biochemical role of B₁₂ and folic acid

- B₁₂ (cobalamin)

- catalyses: intramolecular rearrangement, methylation, reduction of ribonucleotids to desoxiribonucleotids
- *5-desoxycobalamine* (methylmalonilCoA – succinilCoA); abnormal fatty acids↑ and incorporates to neural lipids
- *metilcobalamine* (homocystein – methionin); disorder of folic acid synthesis: DNA synthesis, erythropoesis

- Folic acid

- Coenzyme of C1 units; reduced to tetra- and dihidrofolates

B₁₂ and folic acid metabolism

B₁₂

- Source: liver, meat, eggs
- Intrinsic factor (IF) is produced by parietal cells of stomach
- B12 + IF: absorption in terminal ileum
- Storage: 2 mg in liver, 2 mg outside of it; *enough for 3 years*
- Daily need: 5 µg

Folic acid

- Source: vegetables, liver
- Poliglutamate is deconjugated to monoglutamate in small intestine (difenilhidantoin, AC!)
- Absorbed from jejunum
- Storage: 5 mg in liver, *enough for 3 months*
- Daily need: 400 µg

Causes of B₁₂ deficiency

- Decreased intake (vegetarians)
- Lack of IF
 - After resection of stomach
 - Pernicious anaemia (PA): antibodies against parietal cells and IF, A-type atrophic gastritis
- Bowel diseases with malabsorption (M.Crohn, resection of ileum)
- Increased need (*Diphyllobotrium latum*)
- Bacterial overgrowth, „blind loop syndrome”

Causes of folic acid deficiency

- Malnutrition (alcoholists, old people, psychiatric patients)
- Increased need (haemolysis, pregnancy)
- Malabsorption
- Deconjugation problem caused by drugs (phenytoin)
- Folic acid antagonist therapy (methotrexat, pyrimethamin, trimethoprim, triamteren)

Clinical aspects of B₁₂ and folic acid deficiency

B12

- Macrocytic anaemia (MCV↑↑), pancytopenia, indirect SeBi↑, LDH↑↑↑, ovalo-macrocytosis, hypersegmented gr.
- GI tsymptoms
 - „A”-type atrophic gastritis in PA
 - Hunter glossitis
- Neurologic symptoms
 - Posterior tract: spinal ataxia
 - Pyramid pathway: spastic paresis
 - Psychotic symptomsCan present without anaemia!

Folic acid

- Macrocytic anaemia (MCV↑↑), pancytopenia, indirect SeBi↑, LDH↑↑↑, ovalo-macrocytosis, hypersegmented gr.

Diagnostics of B₁₂ and folic acid deficiency

B₁₂

- History, clinical features
- CBC, Lab
- B₁₂ level
- BM: E hyperplasia, megaloblastic alteration, blockade of maturation, giant stab
- Schilling-test
- AB against parietal cells (>90%), AB against IF (70%), AB against thyroid (40%)
- Gastroscopy, biopsy

Folic acid

- History, clinical features
- CBC, Lab
- Folic acid level (serum and RBC)
- BM: E hyperplasia, megaloblastic alteration, blockade of maturation, giant stab
- Schilling-test negative

Treatment of B₁₂ and folic acid deficiency

B12

- Causal therapy
- 300 µg im. q.o.d. for 2 w, than 3×300 µg weekly for 2 w, than 1×300 µg monthly life long
- HD oral oral (2000 µg/die), for prevention (1% of it is absorbed)
- Potassium and iron supplementation!
- CBC will improve after 1 week: SeBi↓, LDH↓, reticulocyte↑↑; hgb/hct↑; thrombophilia!
- In PA yearly gastroscopy!

Folic acid

- Causal therapy
- 5-10 mg po. q.o.d.
- Potassium and iron supplementation!
- CBC will improve after 1 week: SeBi↓, LDH↓, reticulocyte↑↑; hgb/hct↑; thrombophilia!
- Prevention for pregnant!